to an apparatus for diagnosing a skin condition. The method includes placing a probe, which comprises a plurality of electrodes, against a skin surface of a subject. Each electrode has a plurality of spikes. The spikes are laterally spaced apart from each other, are of a sufficient length, and are adapted to penetrate the stratum corneum (see claims 14 and 30). A first electrode and a second electrode of the plurality of electrodes are spaced from each other a first distance and the second electrode and a third electrode of the plurality of electrodes are spaced a second distance from each other. An electric current is separately passed between the first and second and between the first and third electrodes to obtain at least a first value of impedance and a second value of impedance. Reference data are used to determine whether the impedance value indicates a diseased condition.

Novel features of the present method which distinguish it over the prior art include the use of a plurality of spiked electrodes, where each electrode contains a number of spikes. A second distinguishing feature is that the spikes are adapted to penetrate the stratum corneum. A further distinguishing feature of the present method is the use of at least three electrodes, each having a number of spikes, in which electrical current is passed between a first and second electrode, both having a number of spikes and between a first and third electrode, containing a number of spikes, to measure first and second impedance, as recited.

Using the novel method, the present invention allows one to accurately and easily diagnose a diseased condition of the skin. As one of ordinary skill in the art would readily appreciate, determining a diseased condition of skin using an electronic diagnostic tool, such as the present electric conducting probe, is a complicated matter,

requiring one to accommodate both the electronics of an electrical conducting probe, as well as the anatomy of the skin.

It must be stressed that the human skin is among the most complex organs of the human body. Provided in Figure 1 of Attachment A is a cross-section of the outermost part of the skin of a human being. As can be seen, the skin is enormously complex. It is easily understood that it is of vital interest to reach the layers and structures that actually contain critical information regarding the disease being monitored or diagnosed, while at the same time avoiding information from other layers and structures, which are not relevant to this diagnosis, from being captured or, in the alternative, significantly filtered away so as not to act as an artifact.

The present method allows for measuring electrical current which passes through various depths of the skin to measure impedance at different layers by using the claimed plurality of electrodes, each with a number of spikes. Figure 3, Attachment C, shows the principle of the depth selection, in accordance with the present invention, and Figure 4, Attachment D, shows that the number of spikes per electrode measure impedance at different layers of the skin. As will be apparent to one skilled in the art from Figures 3 and 4, the number of spikes allow current to pass on different paths through different layers of the skin. Moreover, as is shown in Figure 4, the presently claimed method, with spikes passing through the stratum corneum, inherently results in current paths which reach different depths of the skin to reach different parts of the epidermis and the dermis.

Further, highlighting the novel and non-obvious advantage of using electrodes, <u>each having a number of spikes per electrode</u>, versus a probe not having multiple

spikes (e.g., prior art electrodes, such as the one in Davies) is provided in Figure 2, Attachment B, which illustrates the difference between impedance measurements conducted by means of a probe comprising an electrode having a number of spikes and a conventional non-invasive probe, such as the one of Davies. The diagram on the right shows the impedance measure using the minimally invasive probe, according to the present invention, and the diagram on the left shows the impedance measure using a conventional non-invasive probe. As will be noted, the impedance is significantly lower when using the minimally invasive probe, as can be seen with a factor of about 100 and, in addition, the depth penetration is significantly improved. Accordingly, the present method provides features and advantages not found in the art, which include an improved method of diagnosing a diseased skin condition.

Referring now to the art cited in the obviousness-type rejection, Davies discloses a method and system for detecting electrophysiological changes using an electrode which is placed <u>on the surface of a patient's tissue</u> which is to be examined. When using the Davies method and system for diagnosis of a skin disease, impedance is measured through the stratum corneum, and also includes the stratum corneum. Davies fails to teach or in any way recognize any issue associated with current passing through the stratum corneum and fails to identify or note any problem with the use of its electrode or limitations of using an electrode placed on the surface of the tissue to be examined using electrical impedance.

Moreover, one skilled in the art having a thorough understanding of the anatomy of the skin, as well as the disclosure in Davies, would recognize that if the system of Davies is applied to the skin of a subject, even if the penetration depth can be adjusted

by spaced electrodes so that the current may reach the skin layer beneath the stratum corneum, where the most valuable information about the skin condition can be obtained, the current must still pass through the stratum corneum. Thus, important information about skin cancer will be overshadowed by irrelevant information from the stratum corneum. As a result, data collected would not lead to an accurate skin condition diagnosis. In particular, the Davies reference fails to address the aforementioned problem with current passing through the stratum corneum which will result in irrelevant information being obtained which may affect diagnosis of a diseased condition of the skin. However, unlike Davies, the present invention addresses previously unaddressed issues in the art, such as Davies, which fails to recognize a problem with using its probe or using its probe to diagnose a diseased condition of the skin.

Sieburg discloses an electrical device 10 which includes an array of electrodes 16. Each electrode 16 has a single blunt tip region 34. The Sieburg device is for sending electrical signals on the surface of one's skin by measuring skin impedance at each tip 34 of each electrode 16 (see Sieburg, Figures 1-4 and column 8, lines 4-10 and 31-43). Each electrode 16 with single tip 34 is individually addressed via a conductive trace 20 which leads to a respective contact pad 22 (see Sieburg, Figure 1 and column 8, lines 21-23).

Measurements performed in Sieburg, using individually addressed electrodes 16 with single tip 34 sending respective separate signals, result in a high measurement uncertainty originating from a natural variation of skin impedance which may lead to a false diagnosis and depth profile. Moreover, there fails to be any disclosure that the blunt tips 34 can penetrate one's skin.

Contrary to the obviousness rejection, the combined teachings of Davies and Sieburg fail to teach or in any way make obvious the use of a plurality of electrodes, each electrode having a number of spikes, as claimed. Although the Examiner alleges that Sieburg teaches "electrodes 16 furnished with a number of spikes 34 having a variety of dimensions (see paragraphs [0059], [0061] and [0063])," Sieburg actually teaches a plurality of electrodes 16, each having a single spike 34. Therefore, Sieburg fails to teach or in any way make obvious an individual electrode 16 having more than one spike 34. Accordingly, Sieburg, individually or in combination with Davies, fails to teach or in any way make obvious the claimed electrodes, each having a number of spikes.

Moreover, Davies in view of Sieburg fails to teach or in any way make obvious a method in which an electrode has the claimed spike length, e.g., as recited in claim 23, a length which can penetrate the stratum corneum, or even a spike adapted to penetrate the stratum corneum (see, e.g., claim 30).

Furthermore, it would not have been obvious to one of ordinary skill in the art to modify the device of Sieburg to make electrode 16 have more than one spike. There fails to be any disclosure within Sieburg which would lead one of ordinary skill in the art to modify its electrode 16 with a single spike 34 to have more than one spike 34 per electrode 16. For example, there fails to be any disclosure which would lead one of ordinary skill in the art to believe there would be any benefit to having more than a single spike 34 per electrode 16. Further, Sieburg fails to identify any problem or issue associated with having a single spike per electrode which would lead one of ordinary skill in the art to modify electrode 16 of Sieburg.

In addition, as will be apparent to one of ordinary skill in the art, one would not refer to device 10, which comprises a plurality of electrodes 16, as a single electrode comprising a plurality of spikes. More importantly, Sieburg clearly teaches that device 10 is not a single electrode comprising a plurality of spikes 16; Sieburg teaches that device 10 comprises a plurality of electrodes 16, each one being individually addressed at lead 20. Accordingly, one of ordinary skill in the art would not refer to device 10, which comprises an array of electrodes 16, each having a single spike 34, as a single electrode comprising a plurality of spikes 16/tip 34. Accordingly, device 10 fails to teach or in any way make obvious an electrode having a plurality of spikes, as claimed.

Further, one of ordinary skill in the art would not have been led to selectively choose various elements taught individually in Davies and Sieburg to arrive at the claimed invention. In order to find a combination of previously known individual elements obvious, there must be some apparent reason to combine the known elements in the fashion claimed by the patent at issue. See *KSR Int'l. Co. v. Teleflex Inc.*, 55 U.S. ____ (2007). In other words, one of ordinary skill in the art would have had to have seen a benefit for altering the closest prior art by adding to it or removing from it various elements which define the differences between the prior art and the claims at issue.

Nowhere in Sieburg, or anywhere in the art, is there any teaching or any disclosure which would lead one of ordinary skill in the art to modify its individual electrodes 16 with a single tip 34 to form an electrode 16 having a plurality of tips 34. Sieburg fails to provide any disclosure as to any benefit for having more than a single tip

per electrode. Moreover, there fails to be any reasonably apparent reason why one of ordinary skill in the art would modify Davies' electrode to use a plurality of electrodes, each having a number of spikes.

For example, there fails to be any disclosure in either Davies or Sieburg which would lead one of ordinary skill in the art to believe that there would be any benefit from using an electrode having a number of spikes versus the single electrode with no spikes of Davies or the plurality of electrodes, each having a single tip 34, of Sieburg. Specifically, there fails to be any disclosure which would lead one to believe that there would be a benefit from the claimed measurement of impedance from using at least three electrodes, each having a number of spikes of sufficient length to penetrate the stratum corneum, and measuring impedance by passing an electrical current between a first and second electrode and between a first and third electrode, as claimed.

Furthermore, it would not have been obvious to one of ordinary skill in the art to modify the clear disclosure of Sieburg, which clearly discloses addressing its individual tips 34 in order to obtain impedance measurements at each electrode 16/tip 34. Nowhere in Sieburg is there any teaching or disclosure that its device measures impedance between a first and second electrode and between a first and third electrode, as claimed. To the contrary, Sieburg clearly teaches addressing each individual electrode for measuring impedance at each individual electrode 16.

Moreover, the present method, using the claimed electrode, provides features and advantages not obvious from Davies in view of Sieburg, and thus one would not have been led to modify the Sieburg electrode and the Davies method to arrive at the claimed invention.

Sieburg measures impedance using individually addressed electrodes 16/tips 34 to send a signal separately, resulting in a high level of uncertainty originating from a naturally occurring variation of skin impedance which may lead to false diagnosis and depth profile. Conversely, in the novel and non-obvious method, the problem which may be introduced, if one were to use the device of Sieburg in the method of Davies, is avoided since the number of spikes per single electrode are not individually addressed. In the present invention, each electrode contains a plurality of spikes which measure a larger area than possible when using the single spikes per electrode of Sieburg.

Further, the present invention provides enhanced depth penetration not possible from using the electrodes of Sieburg with the method of Davies. The depth penetration possible when using an individually addressed spike, as disclosed in Sieburg, would be significantly less pronounced in comparison with a probe having a number of spikes, as in the present invention. As discussed above, the present invention achieves unexpected advantages and enhanced accuracy and relevant data using the claimed method, which inherently results in allowing the electric current paths to reach different depths, thus reaching different parts of the epidermis and dermis (see Figures 3 and 4, Attachments C and D, respectively). Conversely, there fails to be any disclosure in Sieburg, where individually addressed electrodes have single spikes, as to how its device would be used, in accordance with the claimed method, to result in the determination of impedance values, as claimed.

As discussed above, the presently claimed method results in current paths which reach different depths, thus reaching different parts of the epidermis and dermis (see, e.g., Figure 4, Attachment D). In order for the Sieburg device, with individually

addressed electrodes 16 with tips 34, to have electric current paths between adjacent electrodes 16 with tips 34 which allow for the inherent depth selection of the present method, the device of Sieburg would have to be modified. For example, the device of Sieburg would require a complex addressing circuit in order to, if even possible, obtain a similar depth selection as the device according to the present invention achieves inherently from the claimed method and as shown in Figures 2, 3 and 4, Attachments B-D, and discussed above. However, it must be stressed that Sieburg fails to teach or in any way make obvious how one would modify Sieburg to have a complex addressing circuit in order to achieve what is inherent from the present method.

Consequently, if one of ordinary skill in the art were to, *arguendo*, combine the teachings of Davies with Sieburg, one would:

i) be taught from Davies that DC electropotential and impedance must be used in combination in order to achieve a sufficiently high accuracy;

ii) be taught from Davies that the accuracy can be improved further by using pharmacological agents;

iii) be taught from Sieburg that arrays of individually addressed needles are of a primary interest for the medical diagnosis of the skin;

iv) be taught from Sieburg that a complex addressing circuit must be designed in order to achieve a satisfactory depth selection capability; and

v) be taught from Sieburg that each spike is manufactured by tearing a bonded bonding wire off so as to generate a pointed portion.

In view of the foregoing, a combination of the teachings of Davies and Sieburg may possibly lead one of ordinary skill in the art to create a device in which individually

addressed spikes are used to measure DC electropotential and the impedance. One would also be taught that in order to more accurately measure the alteration in pre-cancerous and cancerous epithelial tissues, a pharmacological agent may be introduced. The agent may include agonists or antagonists of specific ion transport and electrical activity, ionic substitutions and/or hormonal or growth factor stimulation or inhibition of electrical activity (see Davies, column 7, line 25). Sieburg only discusses <u>individually addressed electrodes</u> within a single spike and a skilled person combining Davies and Sieburg will have no incitement to use any other solution than individually addressed electrodes or spikes.

Consequently, a person of ordinary skill in the art, combining Davies and Sieburg, would at least have to solve the following problems in order to enable one to practice the invention, as claimed, i.e. to achieve the claimed results:

a) the depth selection which is necessary to reach different levels of epidermis will require a complex addressing circuit in order to correctly address different individual spikes;

b) the introduced agent which may include agonists or antagonists of specific ion transport and electrical activity, ionic substitutions and/or hormonal or growth factor stimulation or inhibition of electrical activity may influence the measurements and this influence has to be filtered off; and

c) the Sieburg spikes are <u>too</u> blunt to penetrate the stratum corneum, thus resulting in the impedance measurements as shown in the left diagram of Figure 2, Attachment B.

In view of the foregoing, the combination of Davies with Sieburg fails to provide an enabling disclosure to allow one to practice the invention, as claimed. One of ordinary skill in the art will encounter a number of difficult problems when combining Davies and Sieburg in an attempt to practice the present invention, as claimed. However, there is no teaching or disclosure in Davies or Sieburg that would lead one of ordinary skill to modify the prior art devices of Davies and Sieburg to arrive at the invention, as claimed.

In conclusion, Applicants respectfully submit that the combination of Davies in view of Sieburg fails to teach or make obvious all claim elements, namely the claimed plurality of electrodes, each electrode having a number of spikes of sufficient length, which penetrate the stratum corneum, or pass an electric current between a first and second electrode and between a first and third electrode to measure impedance, as claimed. Further, one of ordinary skill in the art would not combine Davies with Sieburg, as there fails to be any reasonably apparent reason why one of ordinary skill in the art would have been led to modify the electrode of Davies to incorporate aspects of Sieburg to arrive at the claimed method. There fails to be any known benefit from combining Davies with Sieburg, and there fails to be any previously identified problem with the device and method of Davies or the method and device of Sieburg which would have led one of ordinary skill in the art to combine the two references to arrive at the claimed invention. Moreover, even if one were to combine Davies with Sieburg, one would not be enabled to practice the method as claimed to provide the disclosed diagnostic tool. Accordingly, Applicants respectfully request that the rejection to the claims be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

Respectfully submitted,

Date: August 4, 2008

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Attachment A

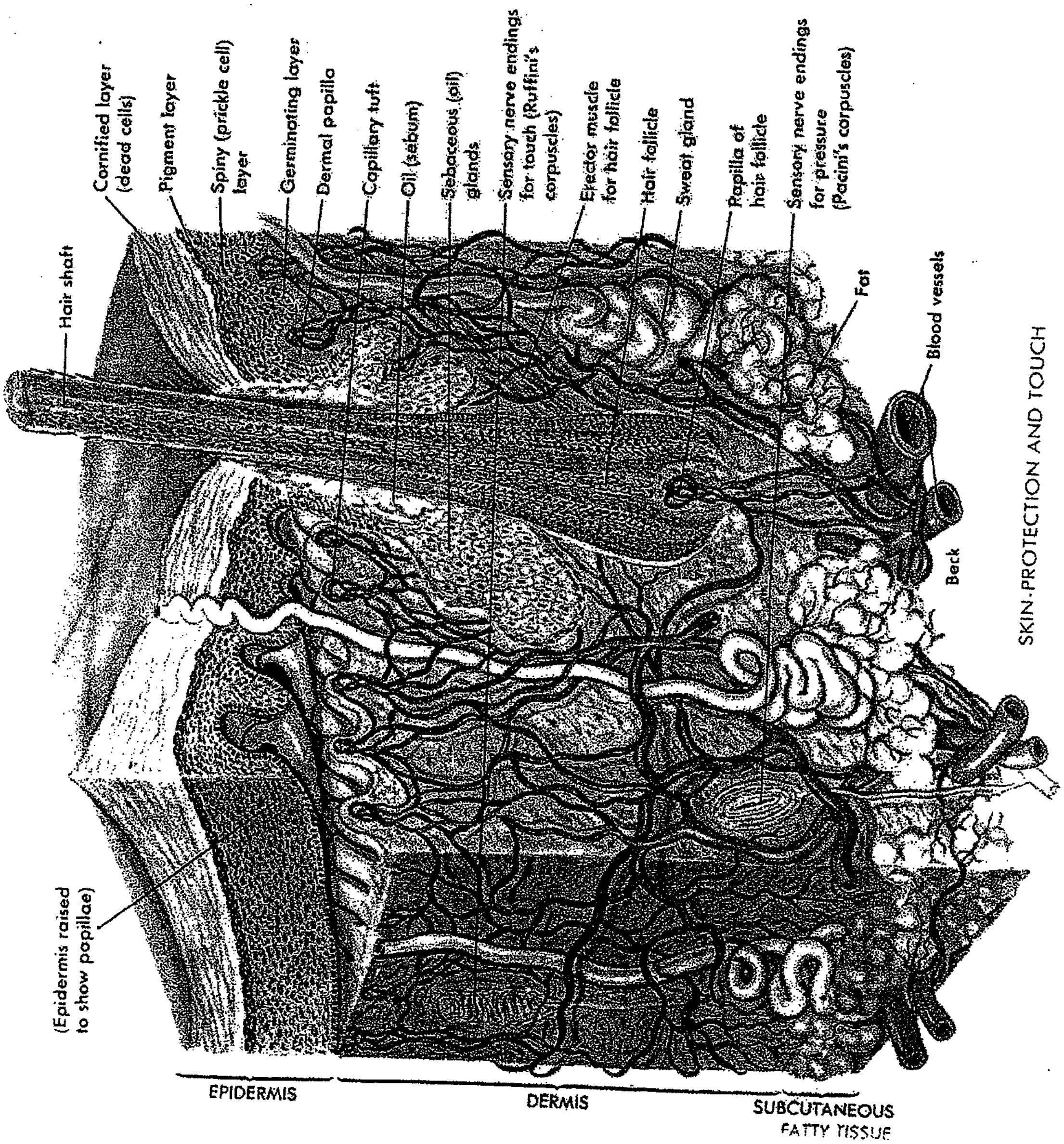
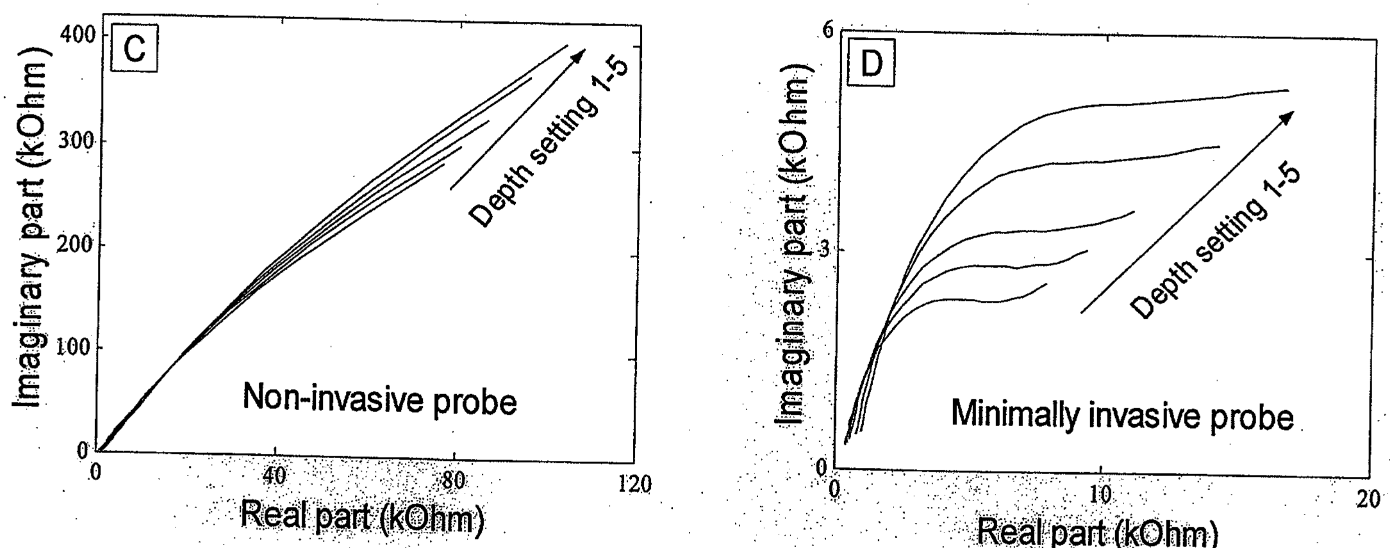


Fig. 1

Attachment B

Karolinska Institutet IEEE SCIBASE

Non-invasive vs. Micro invasive



- Much lower impedance at low frequencies
- More pronounced depth penetration

Fig. 2

Attachment C

Karolinska Institutet

IEEE

SCIBASE

Principle of Depth Selection

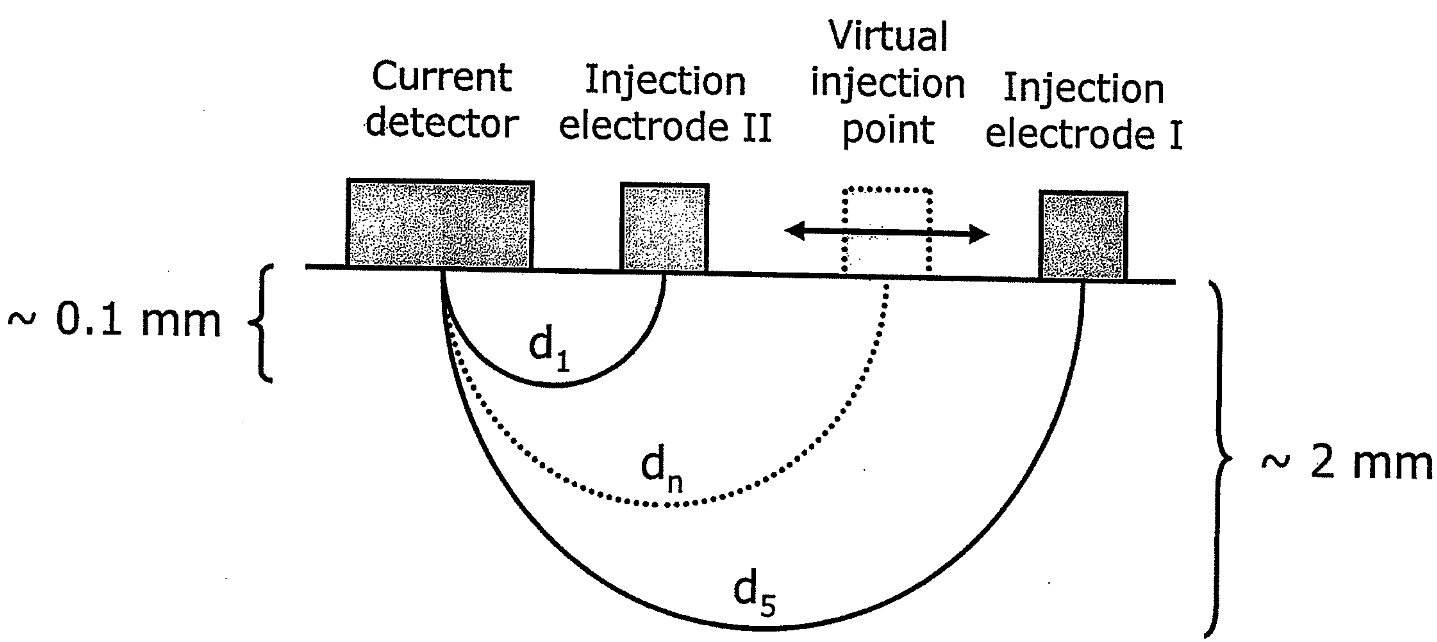


Fig. 3

Attachment D

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IEEE

SCIBASE

Principle of Micro-invasive Impedance

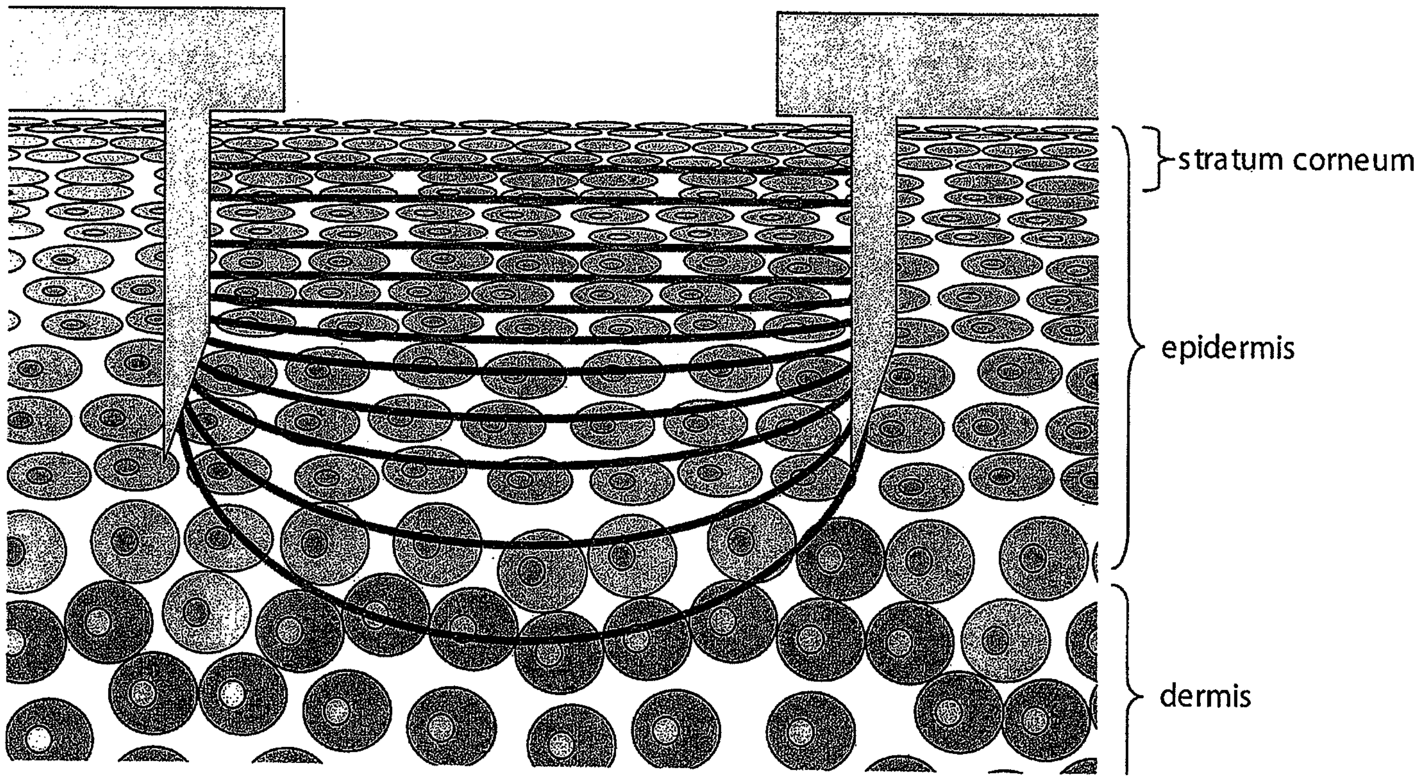

Fig. 4